Title:

Frustrated Ion Pair-Enabled Cross-Electrophile Coupling of Unactivated Alkyl Electrophiles

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Abstract:

Cross-electrophile coupling reactions have evolved into a major strategy for rapidly assembling important molecules, yet challenges remain for the formation of $C(sp^3)$–$C(sp^3)$ bonds that form the core of nearly all organic compounds. Herein, we report a distinct, transition metal-free platform to form such bonds without the need for activating or stabilizing groups on the coupling partners. The reaction is enabled by an unusual single electron transfer in a frustrated ion pair and is complementary in terms of scope to transition metal-catalyzed processes. Moreover, we could further leverage this new mechanistic manifold in the design of other reactions, showing the broad potential of this new reactivity in organic synthesis.

Main Text:

Carbon-based frameworks constitute the backbone of organic molecules that are used in applications ranging from pharmaceuticals to materials. Thus, the modular and efficient construction of C–C bonds is one of the ultimate goals in organic synthesis. Traditionally, cross-coupling reactions between an organometallic reagent and an electrophile have been deployed for this task, leading to the synthesis of numerous essential molecules.(*1, 2*) However, one of the coupling partners usually needs to be pre-functionalized as an organometallic nucleophilic reagent, increasing the step count and requiring handling of potentially sensitive intermediates. In contrast, recently discovered cross-electrophile coupling reactions (XECs) bypass the use of organometallic reagents by directly coupling two electrophilic coupling partners.(*3–5*) XECs are most often catalyzed by transition metals and rely on an external stoichiometric reductant for catalytic turnover. Often, these reactions require at least one coupling partner with $C(sp^2)$ hybridization at the reactive site to control chemoselectivity.(*3, 6*) Forming $C(sp^3)$–$C(sp^3)$ bonds by XECs is significantly more difficult,(*7–10*) but highly desirable due to their ubiquity in organic molecules. For example, the fraction of $C(sp^3)$ atoms in molecules has been positively correlated with clinical success of drug candidates, creating an even stronger demand for $C(sp^3)$–$C(sp^3)$ bond forming reactions.(*11–13*) A challenge in transition metal-catalyzed $C(sp^3)$–$C(sp^3)$ XECs is the propensity to form homo-coupling side-products instead of the desired hetero-coupling products (Fig. 1A).(*14*) This unwanted reactivity can be partially reduced by using a large excess of one of the coupling

partners, leading to additional waste.(*15*) Combined with the negative economic and environmental impact of transition metals, the development of alternative, transition metal-free strategies is highly desirable. This would also improve the scope of C(sp^3)–C(sp^3) XECs to include functional groups that are reactive under many metal-catalyzed conditions or that could poison a metal catalyst. In this context, two seminal reports emerged within the last year that used either electrochemical or enzymatic platforms to enable this highly challenging reactivity (Fig. 1B).(*16*, *17*) These approaches rely on the formation of radical or anionic intermediates from one of the substrates that can then be engaged in C–C bond formation with the second coupling partner. To avoid undesired side reactions of these highly reactive intermediates, stabilizing substituents, e. g. amides or aromatics, are required, inherently restricting these approaches in their reaction scope and preventing the use of fully unactivated substrates. Thus, a transition metal-free XEC of two fully unactivated and unstabilized C(sp^3) coupling partners has so far remained elusive, clearly highlighting the limitations of current approaches. There is thus an urgent need for the design of new, strategically distinct mechanistic manifolds that can address these challenges and thereby unlock the immense potential of XECs for the assembly of C(sp^3)–C(sp^3) linkages ubiquitously found across the molecular sciences.

Here, we report the discovery and investigation of an unprecedented cross-electrophile coupling between two completely unactivated C(sp^3) fragments in a transition metal-free protocol. Alkylphosphonium salts are reacted with alkyl halides in the presence of a sterically hindered base as the sole reagent to give rise to the coupled products. Mechanistic studies suggest that the reaction is enabled by an unusual single-electron transfer (SET) in a sterically hindered ion pair that is reminiscent of frustrated Lewis pair radical reactivity.(*18*–*23*)

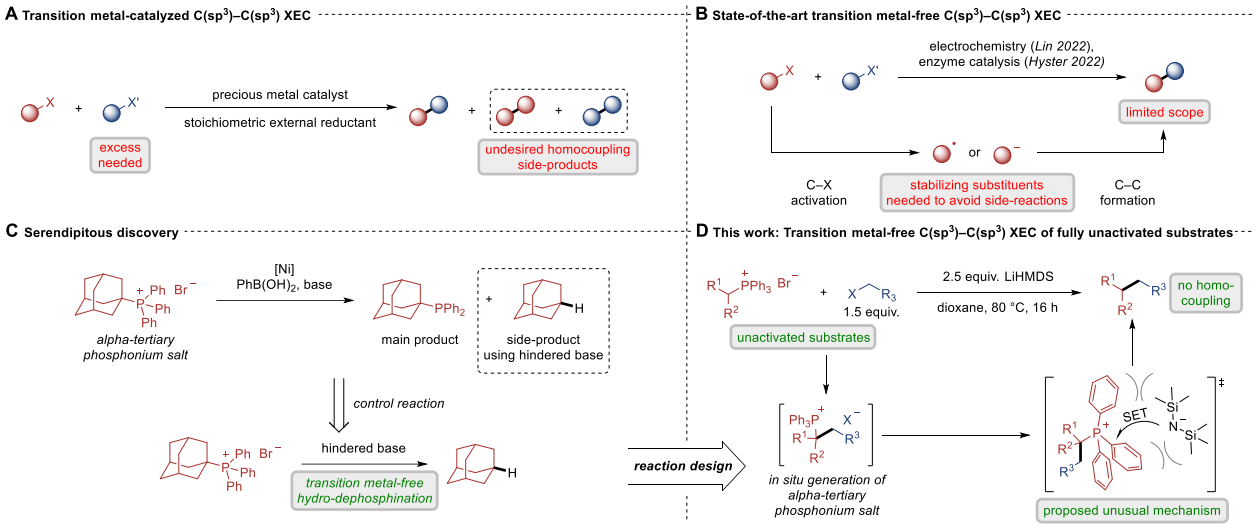

Fig. 1. Context of this work. (**A**) Limitations of transition metal-catalyzed C(sp^3)–C(sp^3) XEC. (**B**) Current methods for transition metal-free C(sp^3)–C(sp^3) XEC. (**C**) Serendipitous discovery of C(sp^3)–P bond activation in phosphonium salts. (**D**) This work: Transition metal-free C(sp^3)–C(sp^3) XEC of unactivated substrates enabled by a frustrated ion pair.

Phosphonium salts are key reagents in organic synthesis. They are readily available and widely used e. g. in the Wittig reaction to construct alkenes.(*24*) Recently, their intriguing reactivity has

also been harnessed in unconventional manners, e.g. for the selective functionalization of heteroarenes.(*25–27*) Additionally, the use of phosphonium salts as C(sp^2) electrophiles in transition metal-catalyzed cross-coupling reactions has been investigated.(*28–32*) Our group has a longstanding interest in diverting the reactivity of phosphonium salts towards unusual transformations, such as C–P metathesis and related transformations for late-stage phosphine functionalization.(*33*, *34*) During our recent studies,(*35*) we discovered conditions under which the P–C(sp^3) bond of the phosphonium salt is activated in addition to the more reactive P–C(sp^2) bond if the phosphonium salt contained a tertiary alkyl group (Fig. 1C). This peculiar hydro-dephosphination sparked our curiosity as it occurred in the absence of any conventional reductant. We reasoned that this unexpected bond activation likely arose from a different mechanism than oxidative addition to the metal catalyst. Our hypothesis was confirmed by subsequent control experiments which demonstrated that the reaction does not require a transition metal catalyst and is mediated by a sterically hindered base. While the nature of the bond activation was unclear at this stage, we aimed to leverage this new reactivity to design a novel approach to challenging C(sp^3)–C(sp^3) bond formation. We hypothesized that an alpha-tertiary alkylphosphonium salt could be formed *in situ* by the alkylation of a phosphorus ylide, which can be generated through the deprotonation of a phosphonium salt. Subsequent base-mediated hydro-dephosphination would enable an overall cross-electrophile coupling that does not require the presence of a transition metal catalyst.

Initial experiments using phosphonium salts and alkyl iodides as the alkylating agent indeed confirmed our hypothesis, as the XEC product was obtained in moderate yields using sterically hindered bases. After careful optimization (see SI, Tables S1–5), we developed a highly efficient transition metal-free formal XEC between unactivated *sec*-alkylphosphonium salts and unactivated alkyl halides which is mediated by lithium hexamethyldisilazide (LiHMDS) as the only added reagent (Fig. 1D).

As the reaction, in contrast to other XEC reactions, does not contain an obvious reductant and the mode of C–P bond activation is unconventional, we became interested in understanding the origin of this unique reactivity. As a first finding, we noticed that triphenylphosphine (**5**), the expected byproduct from a traditional reductive C–P bond activation, was only formed in small amounts (9% nuclear magnetic resonance (NMR) yield), whereas dibenzophosphole **4** was the main byproduct of the reaction in 86% NMR yield, suggesting that the phosphonium moiety serves as a reductant by oxidation of two phenyl C–H bonds to a C–C bond in dibenzophosphole **4** (Fig. 2A). Reaction monitoring by NMR spectroscopy also showed that the phosphonium salt **1** is rapidly deprotonated to its ylide in the presence of LiHMDS (see SI, Fig. S7). When the phosphonium salt **1**, LiHMDS, and alkyl iodide **2** are reacted at room temperature, the *tert*-alkylphosphonium salt **3** is formed as the main species after a few minutes. The identity of **3** was confirmed by an independent synthesis (see SI). The C–C bond formation is thus fast and proceeds through the alkylation of a phosphorus ylide, as set out in our reaction design. These results also highlight that the phosphonium moiety is crucial for the XEC reactivity as it enables the C–C bond formation

via the ylide and also acts as an internal reductant by the unusual oxidation to the dibenzophosphole **4**.(*22*, *23*) Subjecting the *tert*-alkylphosphonium salt **3** to different bases demonstrated that the formation of product is strongly dependent on the size of the base (Fig. 2B). While LiHMDS provided a high yield of product, smaller amide bases showed significantly lowered yield that decreased with decreasing base size. This demonstrates that the size of the base is not only important to limit undesired S_N2 reactions with the alkyl halide substrate, but also plays an important role in the cleavage of the C–P bond. To further study this key step, which is at the core of this new reaction, we used adamantyltriphenylphosphonium bromide (**7**), a phosphonium salt already containing a tertiary alkyl group, as a model substrate. When **7** was reacted with LiHMDS, adamantane (**9**) was formed in similar yield as the XEC products under the model reaction conditions (see SI). However, adding 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO) as a radical trap to this reaction shut down the formation of adamantane (**9**) and, instead, the TEMPO adduct **8** was isolated in 62% yield, suggesting the formation of *tert*-alkyl radicals in the reaction (Fig. 2C). Interestingly, dibenzophosphole **4** was formed in a similar yield compared to the standard reaction conditions, and its formation was therefore not influenced by the presence of TEMPO. As the formation of dibenzophosphole **4** from the PPh_3 moiety in the starting phosphonium salts requires the loss of two aryl hydrogen atoms, we next subjected phosphonium salt **7-*d*$_{15}$**, containing perdeuterated phenyl groups, to the reaction conditions (Fig. 2D). NMR analysis indicated that the adamantane isolated from this reaction contained 72% deuterium at one of the tertiary positions (**9-*d***).

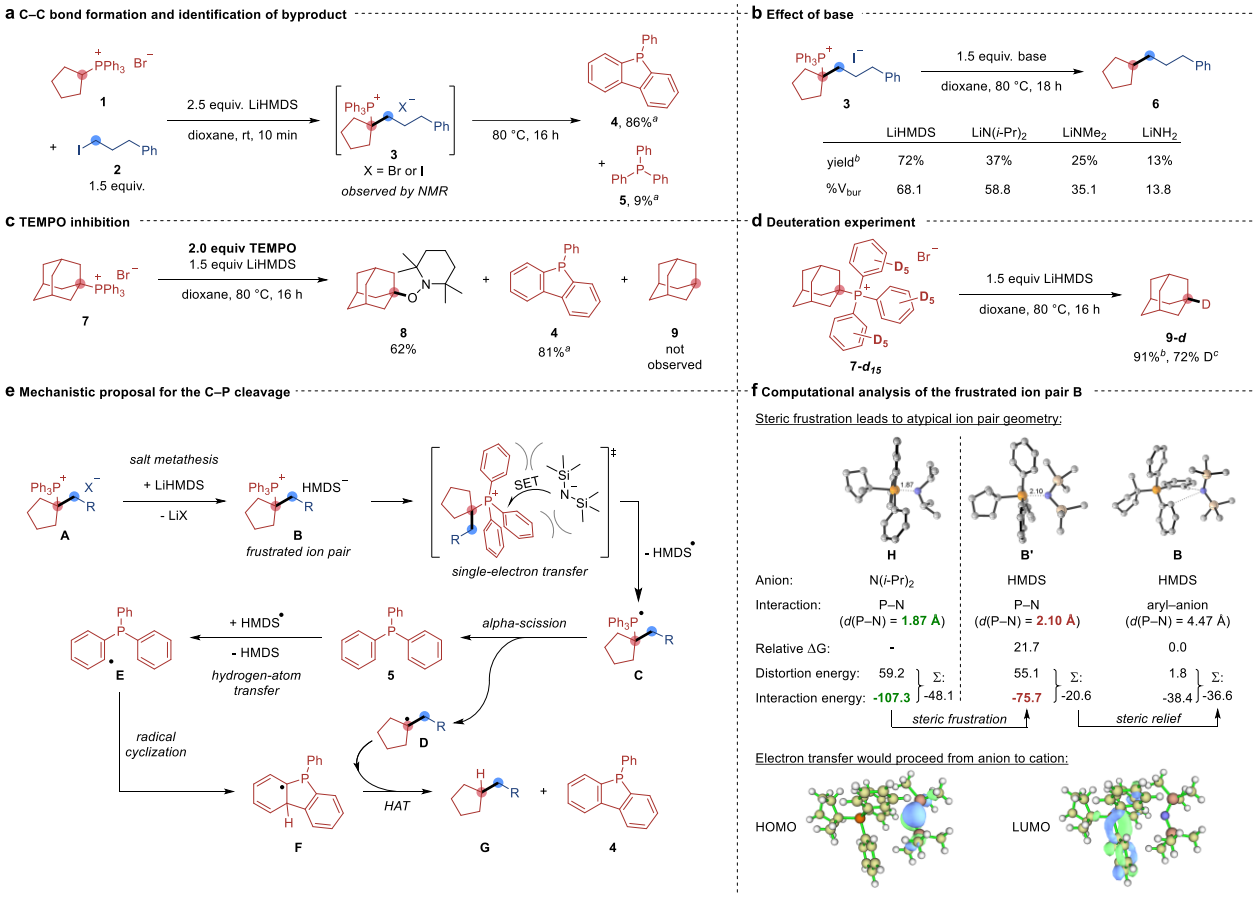

Fig. 2. Mechanistic studies. (**A**) Investigation of the C–C bond formation and identification of the main byproduct. (**B**) Effect of the base size. (**C**) Reaction inhibition by TEMPO. (**D**) Deuteration experiment. (**E**) Proposed mechanism of the C–P cleavage. (**F**) Computed properties of the frustrated ion pair **B**. Energies are in kcal/mol. [a]^{31}P{^{1}H} NMR yield using triphenyl phosphate as internal standard. [b]GC yield using *n*-dodecane as internal standard. [c]Determined by ^{1}H NMR spectroscopy of the isolated material.

With these results in hand, we propose a plausible reaction mechanism (Fig. 2E). The starting phosphonium salt is deprotonated by LiHMDS, and the resulting ylide is rapidly alkylated by the alkyl halide to yield the alpha-tertiary phosphonium salt **A**. Next, salt metathesis between **A** and LiHMDS takes place first, leading to a sterically encumbered ion pair **B**. Experiments using different alkali HMDS salts showed that the presence of lithium ions is important for the reaction, possibly because the formation of LiX (X = Br or I) serves as a driving force for the salt metathesis step. Similarly, addition of 12-crown-4 to the reaction, which selectively binds lithium ions,(*36*) shut down the reactivity (see SI, Table S12). The key step enabling the XEC reaction is a single-electron transfer (SET) from the HMDS anion to the phosphonium cation in the frustrated ion pair **B**. While SET processes in phosphonium halide salts are well known to occur photochemically,(*37–41*) the thermal process has only been postulated for the reaction of tetraphenylphosphonium chloride with lithium amides based on preliminary data.(*22*, *23*) However, no applications or detailed studies of such a process exist so far.

In the lowest energy isomer of the salt **B**, the HMDS anion forms a C-H–anion interaction with a phenyl group of the phosphonium ion and an additional π–anion interaction with a second phenyl group (Fig. 2F). Isomers with direct interaction of the phosphonium P atom and the anion in a

phosphorane-type geometry (isomer **B'**), that are typical for smaller nucleophiles, are significantly higher in energy.(*25*) We performed distortion-interaction analyses on the different phosphonium HMDS ion pair geometries and a related smaller ion pair containing the N(*i*-Pr)$_2$ anion (structure **H**) to understand the origin of the unusual isomer preference. The analysis showed that phosphorane-like isomer **B'** of the HMDS ion pair is destabilized because the interaction energy is significantly lower than in the case of the smaller N(*i*-Pr)$_2$ ion pair **H** (-75.7 kcal/mol and -107. kcal/mol, respectively). This is caused by the large steric bulk of the two ions that leads to a longer P–N distance in the HMDS ion pair **B'** (2.10 Å) than in the N(*i*-Pr)$_2$ ion pair **H** (1.87 Å). Because of this steric frustration, the formation of the atypical phosphonium amide ion pair **B** containing interactions between the HMDS anion and the phosphonium phenyl groups becomes favored. Analysis of the frontier orbitals of **B** shows that the HOMO is located on the HMDS anion whereas the LUMO is delocalized on the phosphonium cation, in line with the direction of the proposed electron transfer. Calculations of the redox potentials of the ions in **B** show that the proposed SET is accessible under the experimental conditions (see SI, Table S14). The SET step would be preceded by the formation of a charge-transfer complex.(*42*, *43*) Indeed, strong charge-transfer bands at ca. 380 nm and 515 nm, potentially arising from such an interaction, were visible by UV/Vis spectroscopy when the phosphonium salt **7** was mixed with LiHMDS (see SI, Fig. S8). A calculated UV/Vis spectrum of **B** shows a charge-transfer band at 348 nm, matching one of the experimentally observed bands well. In contrast, conformer **B'** is predicted to have little charge-transfer character (272 nm). This suggests that **B** is more likely the active ion pair leading to SET, and its formation is enabled by the steric frustration in the phosphonium HMDS ion pair.
The SET step leads to the formation of a phosphoranyl radical **C** and an HMDS radical. Alpha-scission of **C** forms the tertiary alkyl radical **D** and triphenylphosphine (**5**). The highly reactive HMDS radical can abstract a hydrogen atom from triphenylphosphine (**5**), resulting in the aryl radical **E** which can undergo intramolecular cyclization to the cyclic radical **F**. The highlighted weak C–H bond in **F** can be abstracted by the previously generated alkyl radical **D** to aromatize the phosphorus-containing ring system to the experimentally observed byproduct **4** and leading to the XEC alkane product **G**. The proposed pathway is supported by additional DFT calculations (see SI).

Having gained increased understanding of the reaction mechanism, we explored the scope of the reaction (Fig 3). Reacting phosphonium salts with an almost equimolar amount of alkyl halides in the presence of LiHMDS provided a large variety of C(sp^3)–C(sp^3)-coupled products without forming homocoupling side-products that are problematic under transition metal-catalyzed conditions. Phosphonium salts containing differently sized cyclic alkyl groups afforded the XEC product (**12a**–**e**). Smaller-ring electrophiles provided higher yields (**12a**–**c**) than larger-ring or acyclic ones (**12d–f**). Protected amines and alcohols as well as ether moieties were well tolerated (**12g**–**i**). Groups that would be reactive under many transition metal-catalyzed conditions, namely aryl halides (**12j–l**) and aryl boronates (**12m**), gave rise to the XEC products. The reaction also tolerates the presence of heterocycles such as pyrimidines (**12n**) or phenoxazines (**12o**). An indole-containing substrate only provided low yield of the product **12p**, presumably because of the low

tolerance of the acidic C2-position of the indole. In fact, a substrate containing a C2-substituted indole gave much higher yield of the desired product (**12q**) than the substrate containing the unsubstituted indole (**12p**). While the reaction works best using alkyl iodides as coupling partners, alkyl bromides provide the product in similar yield (79% vs. 81% for **12a**). Alkyl tosylates could also be engaged and gave the product in fair yield (**6**, 62%), providing an opportunity to use alcohol starting materials in the reaction after facile derivatization to the corresponding tosylate. Alkyl chlorides participated in the reaction as well, albeit in lower yields (**6**, 32%). Engaging the homobenzylic iodide **11r** as a coupling partner unexpectedly led to the isolation of the spirocyclopropane **12r** in 44% yield instead of the XEC product. We hypothesize that the corresponding styrene of **11r** is formed by a fast E2 elimination to which the *in situ* formed phosphorus ylide can add. This would give rise to a benzylic carbanion that can undergo 1,3-elimination with the phosphonium moiety to form the cyclopropane ring.(*44*)

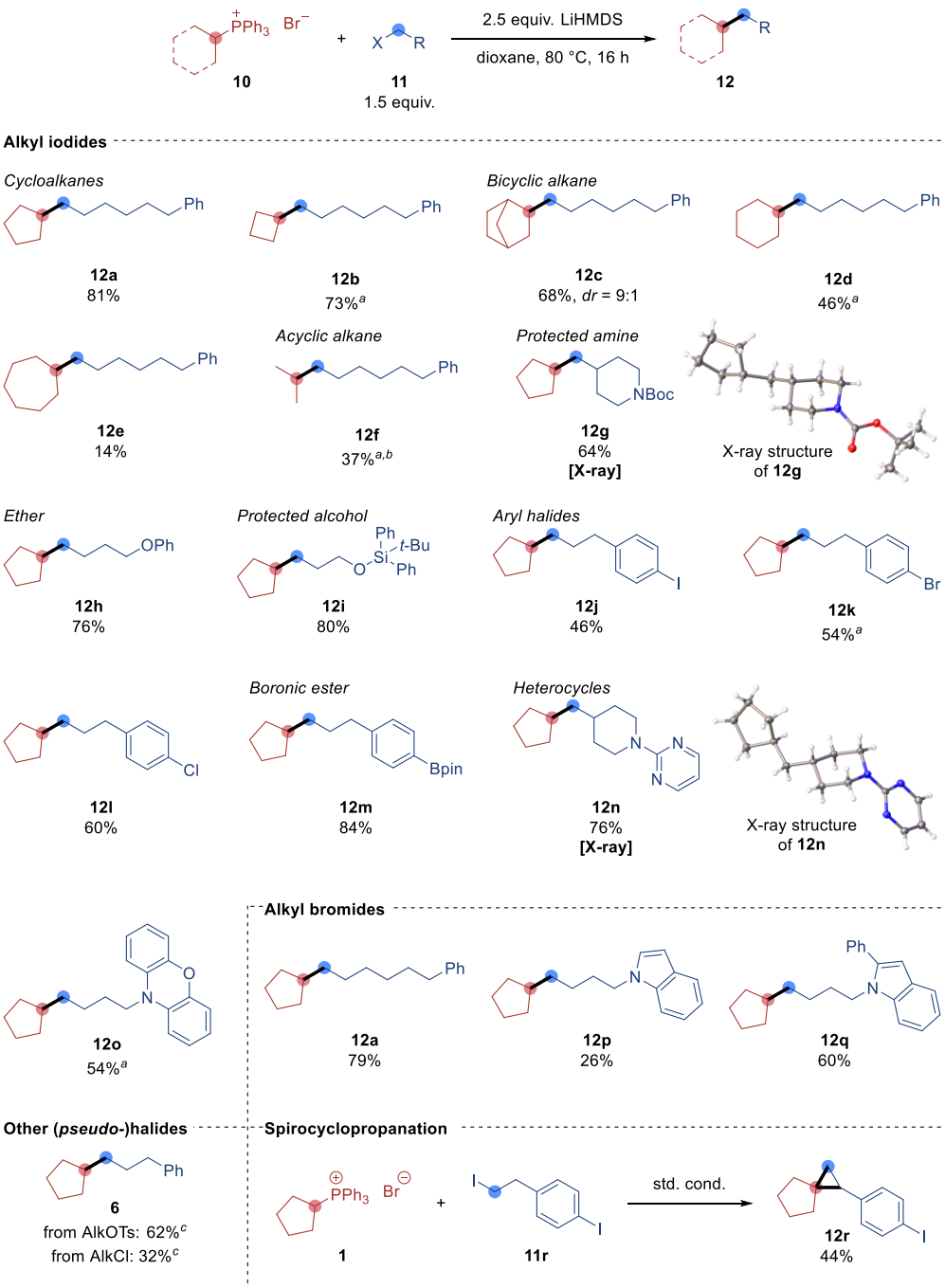

Fig. 3. Scope of the XEC reaction. Yields refer to isolated compounds if not stated otherwise. [a]Isolated after hydroboration-oxidation treatment of the crude reaction mixture. [b]Phosphonium iodide as starting material. [c]GC yields using *n*-dodecane as internal standard.

Using the insights gained from the mechanistic study, we were able to leverage this new reactivity beyond XEC in a series of preliminary results (Fig. 4). Based on the knowledge that the new C–C bond is formed by alkylation of a phosphorus ylide, we also devised a formal [1+n]-cyclization of *n*-alkylphosphonium salt **13** and 1,ω-dibromoalkane **14** (Fig. 4). In this reaction, NaH-mediated phosphorus ylide alkylation occurs twice,(*45*) leading to the same *tert*-alkylphosphonium salt

intermediate as in the standard reaction that can then undergo C–P fragmentation in the presence of LiHMDS. Besides this two-electron process leveraging the phosphorus ylide reactivity, we also utilized the one-electron reactivity of the alkyl radical intermediate for further functionalization. First, we were able to intercept it with styrene **15** to construct a quaternary carbon center in **16**, forming two new C(sp^3)–C(sp^3) bonds in a single step. Leveraging the HAT step of the *tert*-alkyl radical with the phosphonium phenyl groups, the coupling of a phosphonium salt containing perdeuterated phenyl groups (**1-*d*$_{15}$**) led to the formation of the monodeuterated product **12n-*d***. The deuteration is regioselective for the position at which the phosphorus was bound in the starting material over multiple other sites that would be prone to deuteration reactions using conventional approaches.(*46*)

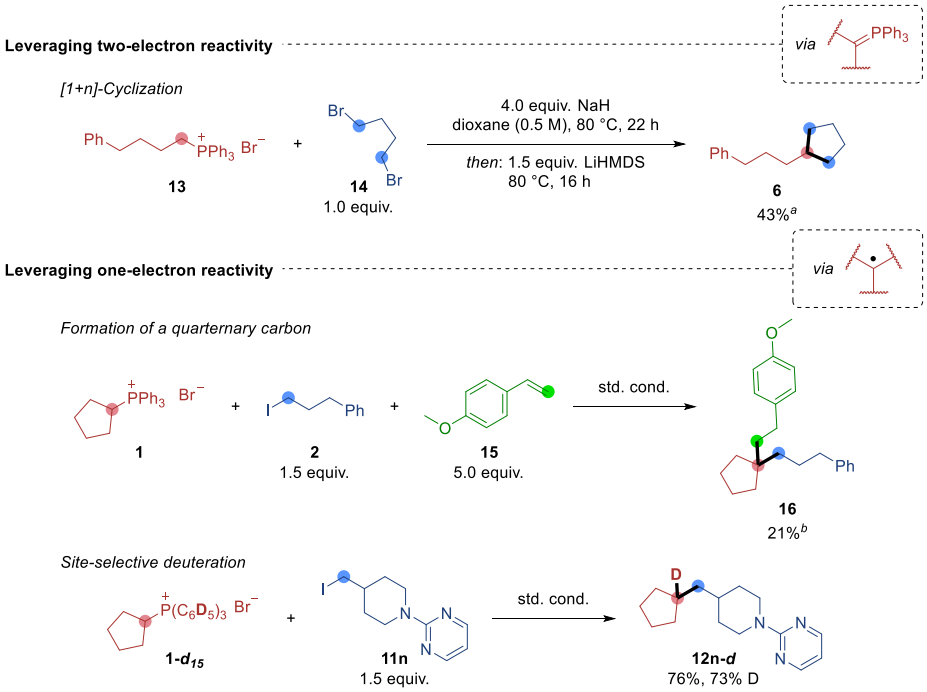

Fig. 4. Mechanistically informed extensions of the reaction scope. [a]GC yield using *n*-dodecane as internal standard. [b]Isolated after hydroboration-oxidation treatment of the crude reaction mixture.

In conclusion, we demonstrated a transition-metal free approach to XEC that allows to couple fully unactivated C(sp^3) electrophiles through an unprecedented mechanistic manifold. The reaction scope includes several functional groups that would be challenging under transition metal catalysis, broadly extending the utility of XEC reactivity. In a broader context, we expect the unusual frustrated ion pair reactivity uncovered in this work to inspire creative solutions to further challenging synthetic problems in organic chemistry.

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Author contributions: S.R discovered the reactivity and designed the project. S.R. and P.B. performed the experimental studies. S.R. performed the DFT studies. B.M. supervised the research. S.R. wrote the original draft of the manuscript which was edited and approved by all authors.

Competing interests: The authors declare no competing interests.

Data and materials availability: X-ray data for compounds **12g** and **12n** are available at the Cambridge Crystallographic Data Centre under the deposition numbers 2254109 and 2254108, respectively.

Supplementary Materials:

Materials and Methods

Supplementary Text

Figs. S1 to S15

Tables S1 to S16

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